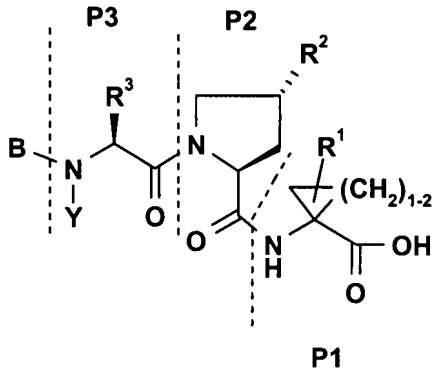
VERSION OF CLAIMS WITH MARKINGS TO SHOW CHANGES MADE

1. (twice amended) ~~A compound of formula (I) comprising~~ The racemates, diastereoisomers ~~and~~ or optical isomers of a compound of formula (I):



(I)

wherein **B** is H, a C_6 or C_{10} aryl, C_{7-16} aralkyl; Het or (lower alkyl)-Het, all of which optionally substituted with C_{1-6} alkyl; C_{1-6} alkoxy; C_{1-6} alkanoyl; hydroxy; hydroxyalkyl; halo; haloalkyl; nitro; cyano; cyanoalkyl; amino optionally substituted with C_{1-6} alkyl; amido; or (lower alkyl)amide; or **B** is an acyl derivative of formula $\mathbf{R_4}$-C(O)-; a carboxyl derivative of formula $\mathbf{R_4}$-O-C(O)-; an amide derivative of formula $\mathbf{R_4}$-N($\mathbf{R_5}$)-C(O)-; a thioamide derivative of formula $\mathbf{R_4}$-N($\mathbf{R_5}$)-C(S)-;or a sulfonyl derivative of formula $\mathbf{R_4}$-SO_2 wherein

$\mathbf{R_4}$ is (i) C_{1-10} alkyl optionally substituted with carboxyl, C_{1-6} alkanoyl, hydroxy, C_{1-6} alkoxy, amino optionally mono- or di-substituted with C_{1-6} alkyl, amido, or (lower alkyl) amide;

(ii) C_{3-7} cycloalkyl, C_{3-7} cycloalkoxy, or C_{4-10} alkylcycloalkyl, all optionally substituted with hydroxy, carboxyl, (C_{1-6} alkoxy)carbonyl, amino optionally mono- or di-substituted with C_{1-6} alkyl, amido, or (lower alkyl) amide;

(iii) amino optionally mono- or di-substituted with C_{1-6} alkyl; amido; or (lower alkyl)amide;

(iv) C_6 or C_{10} aryl or C_{7-16} aralkyl, all optionally substituted with C_{1-6} alkyl, hydroxy, amido, (lower alkyl)amide, or amino optionally mono- or di-substituted with C_{1-6} alkyl; or

(v) Het or (lower alkyl)-Het, both optionally substituted with C_{1-6} alkyl, hydroxy, amido, (lower alkyl) amide, or amino optionally mono- or di-substituted with C_{1-6} alkyl;

R_5 is H or C_{1-6} alkyl; with the proviso that when ~~R_4-~~ B is a carboxyl derivative, an amide derivative or a thioamide derivative, R_4 is not ~~(ii)~~ a cycloalkoxy;

Y is H or C_{1-6} alkyl;

R^3 is C_{1-8} alkyl, C_{3-7} cycloalkyl, or C_{4-10} alkylcycloalkyl, all optionally substituted with hydroxy, C_{1-6} alkoxy, C_{1-6} thioalkyl, amido, (lower alkyl)amido, C_6 or C_{10} aryl, or C_{7-16} aralkyl;

R^2 is CH_2-R_{20}, NH-R_{20}, O-R_{20} or S-R_{20}, wherein R_{20} is pyridinyl, quinolyl, (lower alkyl)-pyridinyl or (lower alkyl)-quinolyl, each optionally mono-, di- or tri-substituted with R_{21},

wherein each R_{21} is independently C_{1-6} alkyl; C_{1-6} alkoxy; lower thioalkyl; sulfonyl; NO_2; OH; SH; halo; haloalkyl; amino optionally mono- or di-substituted with C_{1-6} alkyl, C_6 or C_{10} aryl, C_{7-14} aralkyl, Het or (lower alkyl)-Het; amido optionally mono-substituted with C_{1-6} alkyl, C_6 or C_{10} aryl, C_{7-14} aralkyl, Het or (lower alkyl)-Het; carboxyl; carboxy(lower alkyl); C_6 or C_{10} aryl, C_{7-14} aralkyl or Het, said aryl, aralkyl or Het being optionally substituted with R_{22};

wherein R_{22} is C_{1-6} alkyl; C_{3-7} cycloalkyl; C_{1-6} alkoxy; amino optionally mono- or di-substituted with C_{1-6} alkyl; sulfonyl; (lower alkyl)sulfonyl; NO_2; OH; SH; halo; haloalkyl; carboxyl; amide; (lower alkyl)amide; or Het optionally substituted with C_{1-6} alkyl;

R^1 is H; C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, all optionally substituted with halogen;

or a pharmaceutically acceptable salt or ester thereof;

wherein "Het" is defined as a five-membered saturated or unsaturated, including aromatic, heterocycle containing from one to four heteroatoms selected from nitrogen, oxygen and sulfur, wherein said heterocycle is optionally fused to a benzene ring.

5. (amended) A compound of formula I according to claim 1, wherein **B** is a carboxyl derivative of formula R_4-O-C(O)-, wherein R_4 is

(i) C_{1-10} alkyl optionally substituted with carboxyl, C_{1-6} alkanoyl, hydroxy, C_{1-6} alkoxy, amino optionally mono- or di-substituted with C_{1-6} alkyl, amido or (lower alkyl)amide;

(ii) C_{3-7} cycloalkyl, C_{4-10} alkylcycloalkyl, all optionally substituted with carboxyl, (C_{1-6}

alkoxy)carbonyl, amino optionally mono- or di-substituted with C_{1-6} alkyl, amido or (lower alkyl)amide;
(iv) C_6 or C_{10} aryl or C_{7-16} aralkyl optionally substituted with C_{1-6} alkyl, hydroxy, amido, (lower alkyl)amido, or amino optionally mono- or di-substituted with C_{1-6} alkyl; or
(v) Het or (lower alkyl)-Het, both optionally substituted with C_{1-6} alkyl, hydroxy, amino optionally mono- or di-substituted with C_{1-6} alkyl, amido or (lower alkyl)amide.

6. (amended) A compound of formula I according to claim 1, wherein **B** is an amide derivative of formula $\mathbf{R_4}$-N($\mathbf{R_5}$)-C(O)- wherein $\mathbf{R_4}$ is
(i) C_{1-10} alkyl optionally substituted with carboxyl, C_{1-6} alkanoyl, hydroxy, C_{1-6} alkoxy, amido, (lower alkyl)amido, or amino optionally mono- or di-substituted with C_{1-6} alkyl;
(ii) C_{3-7} cycloalkyl or C_{4-10} alkylcycloalkyl, all optionally substituted with carboxyl, (C_{1-6} alkoxy)carbonyl, amido, (lower alkyl)amido, or amino optionally mono- or di-substituted with C_{1-6} alkyl;
(iii) amino optionally mono- or di-substituted with C_{1-3} alkyl;
(iv) C_6 or C_{10} aryl or C_{7-16} aralkyl, all optionally substituted with C_{1-6} alkyl, hydroxy, amido, (lower alkyl)amide, or amino optionally substituted with C_{1-6} alkyl; or
(v) Het or (lower alkyl)-Het, both optionally substituted with C_{1-6} alkyl, hydroxy, amino optionally substituted with C_{1-6} alkyl, amido or (lower alkyl)amide; and
$\mathbf{R_5}$ is H or methyl.

7. (amended) A compound of formula I according to claim 1, wherein **B** is a thioamide derivative of formula $\mathbf{R_4}$-NH-C(S)-; wherein $\mathbf{R_4}$ is
(i) C_{1-10} alkyl optionally substituted with carboxyl, C_{1-6} alkanoyl or C_{1-6} alkoxy;
(ii) C_{3-7} cycloalkyl or C_{4-10} alkylcycloalkyl, all optionally substituted with carboxyl, (C_{1-6} alkoxy)carbonyl, amino or amido.

11. (amended) A compound of formula I according to claim 5, wherein **B** is a carboxyl derivative of formula $\mathbf{R_4}$-O-C(O)-, wherein $\mathbf{R_4}$ is

(i) C_{1-10} alkyl optionally substituted with carboxyl, C_{1-6} alkanoyl, hydroxy, C_{1-6} alkoxy or amido, (lower alkyl)amide, amino optionally mono- or di-substituted with C_{1-6} alkyl;
(ii) C_{3-7} cycloalkyl, C_{4-10} alkylcycloalkyl, all optionally substituted with carboxyl, (C_{1-6} alkoxy)carbonyl, amido, (lower alkyl)amide, amino optionally mono- or di-substituted with C_{1-6} alkyl, or
(iv) C_6 or C_{10} aryl or C_{7-16} aralkyl, all optionally substituted with C_{1-6} alkyl, hydroxy, amino optionally substituted with C_{1-6} alkyl; or
(v) Het or (lower alkyl)-Het, both optionally substituted with C_{1-6} alkyl, hydroxy, amido, or amino optionally mono-substituted with C_{1-6} alkyl.

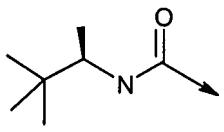
12. (amended) A compound of formula I according to claim 6, wherein **B** is an amide derivative of formula $\mathbf{R_4}$-N($\mathbf{R_5}$)-C(O)- wherein $\mathbf{R_4}$ is
(i) C_{1-10} alkyl optionally substituted with carboxyl, C_{1-6} alkanoyl, hydroxy, C_{1-6} alkoxy, amido, (lower alkyl)amide, amino optionally mono- or di-substituted with C_{1-6} alkyl;
(ii) C_{3-7} cycloalkyl or C_{4-10} alkylcycloalkyl, all optionally substituted with carboxyl, (C_{1-6} alkoxy)carbonyl, amido, (lower alkyl)amide, amino optionally mono- or di-substituted with C_{1-6} alkyl;
(iii) amino optionally mono- or di-substituted with C_{1-3} alkyl, or
(iv) C_6 or C_{10} aryl or C_{7-16} aralkyl, all optionally substituted with C_{1-6} alkyl, hydroxy, amino or amido optionally substituted with C_{1-6} alkyl; or
(v) Het optionally substituted with C_{1-6} alkyl, hydroxy, amino or amido,
and $\mathbf{R_5}$ is H.

13. (amended) A compound of formula I according to claim 7, wherein **B** is a thioamide derivative of formula $\mathbf{R_4}$-NH-C(S)-; wherein $\mathbf{R_4}$ is (i) C_{1-10} alkyl; or (ii) C_{3-7} cycloalkyl.

14. (amended) A compound of formula I according to claim 12, wherein **B** is an amide derivative of formula $\mathbf{R_4}$-NH-C(O)- wherein $\mathbf{R_4}$ is
(i) C_{1-10} alkyl optionally substituted with carboxyl, C_{1-6} alkanoyl, hydroxy, C_{1-6} alkoxy

amido, (lower alkyl)amide, amino optionally mono- or di-substituted with C_{1-6} alkyl;
(ii) C_{3-7} cycloalkyl or C_{4-10} alkylcycloalkyl, all optionally substituted with carboxyl, (C_{1-6} alkoxy)carbonyl, amido, (lower alkyl)amide, amino optionally mono- or di-substituted with C_{1-6} alkyl;
(iv) C_6 or C_{10} aryl or C_{7-16} aralkyl optionally substituted with C_{1-6} alkyl, hydroxy, amino or amido.

15. (amended) A compound of formula I according to claim 1, wherein **B** is

~~*tert* butoxycarbonyl (Boc)~~ or 

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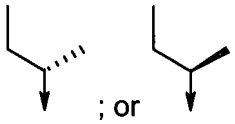
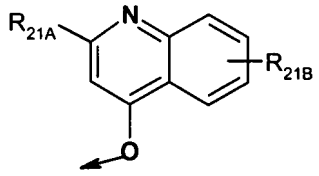
19. (amended) A compound of formula I according to claim 18, wherein $\mathbf{R^3}$ is the side chain of ~~*tert*-butylglycine (Tbg)~~, Ile, Val, Chg or:


; or .

29. (twice amended) A compound of formula I according to claim 26, wherein $\mathbf{R^2}$ is :



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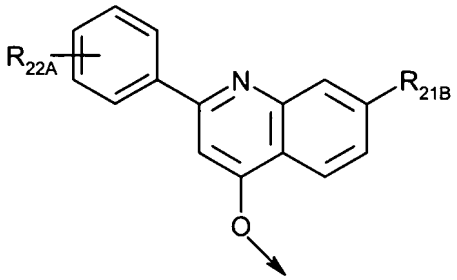
wherein $\mathbf{R_{21A}}$ is C_{1-6} alkyl; C_{1-6} alkoxy; lower thioalkyl; halo; amino optionally mono-substituted with C_{1-6} alkyl; or C_6, C_{10} aryl, C_{7-16} aralkyl, or Het, saisd aryl, aralkyl or Het optionally substituted with $\mathbf{R_{22}}$ wherein $\mathbf{R_{22}}$ is C_{1-6} alkyl, C_{1-6} alkoxy, amido, (lower alkyl)amide, amino optionally mono- or di-substituted with C_{1-6} alkyl, or Het; and
$\mathbf{R_{21B}}$ is C_{1-6} alkyl, C_{1-6} alkoxy, amino, di(lower alkyl)amino, (lower alkyl)amide, NO_2, OH, halo, trifluoromethyl, or carboxyl.

30. (amended) A compound of formula I according to claim 29, wherein $\mathbf{R_{21A}}$ is C_6, C_{10} aryl or Het, all optionally substituted with $\mathbf{R_{22}}$ as defined in claim ~~30~~ 29.

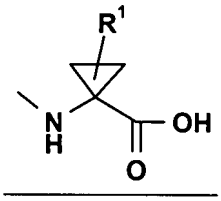
32. (amended) A compound of formula I according to claim ~~29~~21, wherein $\mathbf{R^2}$ is:



wherein $\mathbf{R_{22A}}$ is C_{1-6} alkyl; C_{1-6} alkoxy; or halo; and $\mathbf{R_{21B}}$ is C_{1-6} alkyl, C_{1-6} alkoxy, amino, di(lower alkyl)amino, (lower alkyl)amide, NO_2, OH, halo, trifluoromethyl, or carboxyl.

36. (twice amended) A compound of formula I according to claim 1, wherein ~~P1 is a cyclobutyl or cyclopropyl ring, both optionally substituted with R^1, wherein~~ $\mathbf{R^1}$ is H, C_{1-3} alkyl, C_{3-5} cycloalkyl, or C_{2-4} alkenyl, all optionally substituted with halo.

37. (amended) A compound of formula I according to claim 36, wherein **P1** is: ~~cyclopropyl~~



and $\mathbf{R^1}$ is ethyl, vinyl, cyclopropyl, 1 or 2-bromoethyl or 1 or 2-bromovinyl.

45. (twice amended) A compound of formula I according to claim 1, wherein **B** is a C_6 or C_{10} aryl or C_{7-16} aralkyl, all optionally substituted with C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, hydroxy, hydroxyalkyl, halo, haloalkyl, nitro, cyano, cyanoalkyl, amido, (lower alkyl)amido, or amino optionally substituted with C_{1-6} alkyl; or

Het or (lower alkyl)-Het, all optionally substituted with C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, hydroxy, hydroxyalkyl, halo, haloalkyl, nitro, cyano, cyanoalkyl, amido, (lower alkyl)amido, or amino optionally substituted with C_{1-6} alkyl,. or

B is $\mathbf{R_4}$-SO_2 wherein $\mathbf{R_4}$ is preferably amido; (lower alkyl)amide; C_6 or C_{10} aryl, C_{7-14} aralkyl or Het, all optionally substituted with C_{1-6} alkyl, or

B is an acyl derivative of formula $\mathbf{R_4}$-C(O)- wherein $\mathbf{R_4}$ is

(i) C_{1-10} alkyl optionally substituted with carboxyl, hydroxy or C_{1-6} alkoxy, amido, (lower alkyl)amide, or amino optionally mono- or di-substituted with C_{1-6} alkyl;

(ii) C_{3-7} cycloalkyl or C_{4-10} alkylcycloalkyl, both optionally substituted with hydroxy, carboxyl, (C_{1-6} alkoxy)carbonyl, amido, (lower alkyl)amide, or amino optionally mono- or di-substituted with C_{1-6} alkyl;

(iv) C_6 or C_{10} aryl or C_{7-16} aralkyl, all optionally substituted with C_{1-6} alkyl, hydroxy, amido, (lower alkyl)amide, or amino optionally substituted with C_{1-6} alkyl;

(v) Het or (lower alkyl)-Het, both optionally substituted with C_{1-6} alkyl, hydroxy, amino optionally substituted with C_{1-6} alkyl, amido, (lower alkyl)amide, or amino optionally substituted with C_{1-6} alkyl, or

B is a carboxyl derivative of formula $\mathbf{R_4}$-O-C(O)-, wherein $\mathbf{R_4}$ is

(i) C_{1-10} alkyl optionally substituted with carboxyl, C_{1-6} alkanoyl, hydroxy, C_{1-6} alkoxy, amino optionally mono- or di-substituted with C_{1-6} alkyl, amido or (lower alkyl)amide;

(ii) C_{3-7} cycloalkyl, C_{4-10} alkylcycloalkyl, all optionally substituted with carboxyl, (C_{1-6} alkoxy)carbonyl, amino optionally mono- or di-substituted with C_{1-6} alkyl, amido or (lower alkyl)amide;

(iv) C_6 or C_{10} aryl or C_{7-16} aralkyl optionally substituted with C_{1-6} alkyl, hydroxy, amido, (lower alkyl)amido, or amino optionally mono- or di-substituted with C_{1-6} alkyl; or

(v) Het or (lower alkyl)-Het, both optionally substituted with C_{1-6} alkyl, hydroxy, amino optionally mono- or di-substituted with C_{1-6} alkyl, amido or (lower alkyl)amido, or

B is an amide derivative of formula $\mathbf{R_4}$-N($\mathbf{R_5}$)-C(O)- wherein $\mathbf{R_4}$ is

(i) C_{1-10} alkyl optionally substituted with carboxyl, C_{1-6} alkanoyl, hydroxy, C_{1-6} alkoxy, amido, (lower alkyl)amido, or amino optionally mono- or di-substituted with C_{1-6} alkyl;

(ii) C_{3-7} cycloalkyl or C_{4-10} alkylcycloalkyl, all optionally substituted with carboxyl, (C_{1-6} alkoxy)carbonyl, amido, (lower alkyl)amido, or amino optionally mono- or di-substituted with C_{1-6} alkyl;

(iii) amino optionally mono- or di-substituted with C_{1-3} alkyl;

(iv) C_6 or C_{10} aryl or C_{7-16} aralkyl, all optionally substituted with C_{1-6} alkyl, hydroxy, amido, (lower alkyl)amide, or amino optionally substituted with C_{1-6} alkyl; or

(v) Het or (lower alkyl)-Het, both optionally substituted with C_{1-6} alkyl, hydroxy, amino optionally substituted with C_{1-6} alkyl, amido or (lower alkyl)amide; and

$\mathbf{R_5}$ is H or methyl, or

B is thioamide derivative of formula $\mathbf{R_4}$-NH-C(S)-; wherein $\mathbf{R_4}$ is

(i) C_{1-10} alkyl optionally substituted with carboxyl, C_{1-6} alkanoyl or C_{1-6} alkoxy;

(ii) C_{3-7} cycloalkyl or C_{4-10} alkylcycloalkyl, all optionally substituted with carboxyl, (C_{1-6} alkoxy)carbonyl, amino or amido;

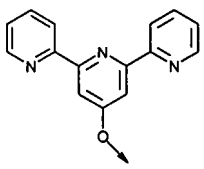
Y is H or methyl;

$\mathbf{R^3}$ is C_{1-8} alkyl, C_{3-7} cycloalkyl, or C_{4-10} alkylcycloalkyl, all optionally substituted with hydroxy, C_{1-6} alkoxy, C_{1-6} thioalkyl, acetamido, C_6 or C_{10} aryl, or C_{7-16} aralkyl;

R^2 is S-$\mathbf{R_{20}}$ or O-$\mathbf{R_{20}}$ wherein $\mathbf{R_{20}}$ is pyridinyl, quinolyl, -CH_2-pyridinyl or -CH_2-quinolyl, all optionally mono-, di- or tri-substituted with $\mathbf{R_{21}}$, wherein

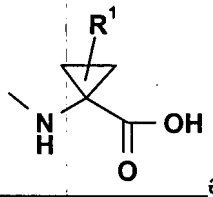
$\mathbf{R_{21}}$ is C_{1-6} alkyl; C_{1-6} alkoxy; lower thioalkyl; amino or amido optionally mono-or di-substituted with C_{1-6} alkyl, C_6 or C_{10} aryl, C_{7-16} aralkyl, Het or (lower alkyl)-Het; NO_2; OH; halo; trifluoromethyl; carboxyl; C_6 or C_{10} aryl, C_{7-16} aralkyl, or Het, said aryl, aralkyl or Het being optionally substituted with $\mathbf{R_{22}}$, wherein

$\mathbf{R_{22}}$ is C_{1-6} alkyl; C_{3-7} cycloalkyl; C_{1-6} alkoxy; amino; mono- or di-(lower alkyl)amino; (lower alkyl)amide; sulfonylalkyl; NO_2; OH; halo; trifluoromethyl; carboxyl or Het; or

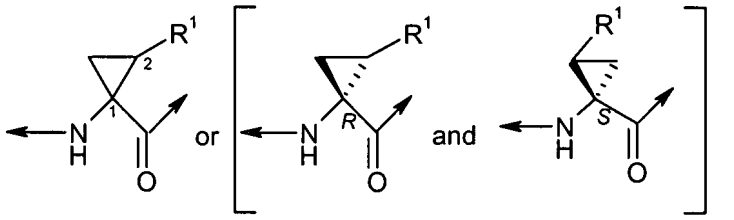
R^2 is  ;

or R^2 is quinolinoxy unsubstituted , mono- or di-substituted with $\mathbf{R_{21}}$ as defined above; and

~~the **P1** segment is:~~



a cyclopropyl ring, both optionally substituted with R^1, wherein R^1 is H, C_{1-3} alkyl, C_{3-5} cycloalkyl, or C_{2-4} alkenyl optionally substituted with halo, and said R^1 at carbon 2 is orientated *syn* to the carbonyl at position 1, represented by the radical:



;

or a pharmaceutically acceptable salt or ester thereof.

46. (twice amended) A compound of formula I according to claim 45, wherein **B** is a C_6 or C_{10} aryl optionally substituted with C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, hydroxy, hydroxyalkyl, halo, haloalkyl, nitro, cyano, cyanoalkyl, amido, (lower alkyl)amide, or amino optionally mono- or di-substituted with C_{1-6} alkyl; or **B** is Het optionally substituted with C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, hydroxy, halo, amido, (lower alkyl)amide, or amino optionally mono- or di-substituted with C_{1-6} alkyl; or

B is R_4-SO_2 wherein R_4 is C_6 or C_{10} aryl, a C_{7-14} aralkyl or Het all optionally substituted with C_{1-6} alkyl; amido, (lower alkyl)amide; **B** is an acyl derivative of formula R_4-C(O)- wherein R_4 is

(i) C_{1-10} alkyl optionally substituted with carboxyl, hydroxy or C_{1-6} alkoxy; or

(ii) C_{3-7} cycloalkyl or C_{4-10} alkylcycloalkyl, both optionally substituted with hydroxy, carboxyl, (C_{1-6} alkoxy)carbonyl; or

(iv) C_6 or C_{10} aryl or C_{7-16} aralkyl, all optionally substituted with C_{1-6} alkyl, hydroxy; or

(v) Het optionally substituted with C_{1-6} alkyl, hydroxy, amido or amino;

or **B** is a carboxyl derivative of formula R_4-O-C(O)-, wherein R_4 is

(i) C_{1-10} alkyl optionally substituted with carboxyl, C_{1-6} alkanoyl, hydroxy, C_{1-6} alkoxy or

amido, (lower alkyl)amide, amino optionally mono- or di-substituted with C_{1-6} alkyl;

(ii) C_{3-7} cycloalkyl, C_{4-10} alkylcycloalkyl, all optionally substituted with carboxyl, (C_{1-6} alkoxy)carbonyl, amido, (lower alkyl)amide, amino optionally mono- or di-substituted with C_{1-6} alkyl; or

(iv) C_6 or C_{10} aryl or C_{7-16} aralkyl, all optionally substituted with C_{1-6} alkyl, hydroxy, amino optionally substituted with C_{1-6} alkyl; or

(v) Het or (lower alkyl)-Het, both optionally substituted with C_{1-6} alkyl, hydroxy, amido, or amino optionally mono-substituted with C_{1-6} alkyl;

or **B** is an amide derivative of formula $\mathbf{R_4}$-N($\mathbf{R_5}$)-C(O)- wherein $\mathbf{R_4}$ is

(i) C_{1-10} alkyl optionally substituted with carboxyl, C_{1-6} alkanoyl, hydroxy, C_{1-6} alkoxy, amido, (lower alkyl)amide, amino optionally mono- or di-substituted with C_{1-6} alkyl;

(ii) C_{3-7} cycloalkyl or C_{4-10} alkylcycloalkyl, all optionally substituted with carboxyl, (C_{1-6} alkoxy)carbonyl, amido, (lower alkyl)amide, amino optionally mono- or di-substituted with C_{1-6} alkyl; and $\mathbf{R_5}$ is H or methyl; or

$\mathbf{R_4}$ is (iii) amino optionally mono- or di-substituted with C_{1-3} alkyl; or

(iv) C_6 or C_{10} aryl or C_{7-16} aralkyl, all optionally substituted with C_{1-6} alkyl, hydroxy, amino or amido optionally substituted with C_{1-6} alkyl; or

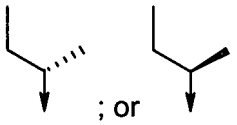
(v) Het optionally substituted with C_{1-6} alkyl, hydroxy, amino or amido; or

B is a thioamide derivative of formula $\mathbf{R_4}$-NH-C(S)-; wherein $\mathbf{R_4}$ is:

(i) C_{1-10} alkyl; or (ii) C_{3-7} cycloalkyl; or

Y is H;

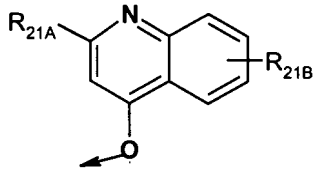
$\mathbf{R^3}$ is the side chain of ~~*tert*-butylglycine (~~Tbg~~)~~, Ile, Val, Chg or:



; or ;

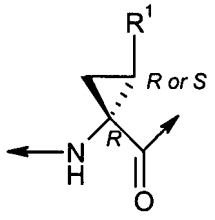
R^2 is quinolinoxy unsubstituted, mono- or di-substituted with $\mathbf{R_{21}}$ as defined above, or

R^2 is :



wherein $\mathbf{R_{21A}}$ is C_{1-6} alkyl; C_{1-6} alkoxy; C_6, C_{10} aryl or Het; lower thioalkyl; halo; amino optionally mono-substituted with C_{1-6} alkyl; or C_6,C_{10} aryl, C_{7-16} aralkyl or Het, optionally substituted with $\mathbf{R_{22}}$ wherein $\mathbf{R_{22}}$ is C_{1-6} alkyl, C_{1-6} alkoxy, amido, (lower alkyl)amide, amino optionally mono- or di-substituted with C_{1-6} alkyl, or Het;

P1 is: ~~a cyclopropyl ring wherein carbon 1 has the *R* configuration,~~



; and

$\mathbf{R^1}$ is ethyl, vinyl, cyclopropyl, 1 or 2-bromoethyl or 1 or 2-bromovinyl.

47. (amended) A compound of formula I according to claim 46, wherein

B is an amide <u>derivative</u> of formula $\mathbf{R_4}$-NH-C(O)- wherein $\mathbf{R_4}$ is

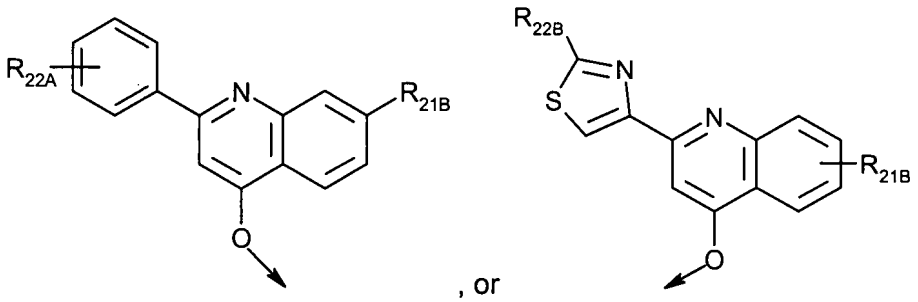
i) C_{1-10} alkyl optionally substituted with carboxyl, C_{1-6} alkanoyl, hydroxy, C_{1-6} alkoxy amido, (lower alkyl)amide, amino optionally mono- or di-substituted with C_{1-6} alkyl;

(ii) C_{3-7} cycloalkyl or C_{4-10} alkylcycloalkyl, all optionally substituted with carboxyl, (C_{1-6} alkoxy)carbonyl, amido, (lower alkyl)amide, amino optionally mono- or di-substituted with C_{1-6} alkyl;

(iv) C_6 or C_{10} aryl or C_{7-16} aralkyl optionally substituted with C_{1-6} alkyl, hydroxy, amino or amido;

$\mathbf{R^3}$ is the side chain of Tbg, Chg or Val;

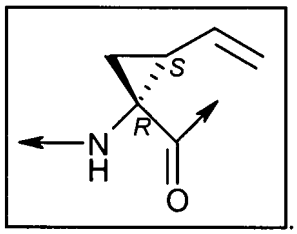
$\mathbf{R^2}$ is:



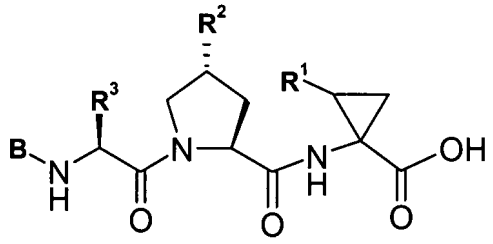
, or

wherein **R_{22A}** is C_{1-6} alkyl ~~(such as methyl)~~; C_{1-6} alkoxy ~~(such as methoxy)~~; or halo ~~(such as chloro)~~; **R_{22B}** is C_{1-6} alkyl, amino optionally mono-substituted with C_{1-6} alkyl, amido, or (lower alkyl)amide; and **R_{21B}** is C_{1-6} alkyl, C_{1-6} alkoxy, amino, di(lower alkyl)amino, (lower alkyl)amide, NO_2, OH, halo, trifluoromethyl, or carboxyl;

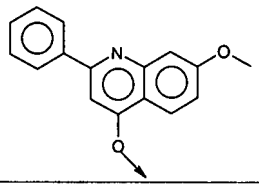
and **P1** is:



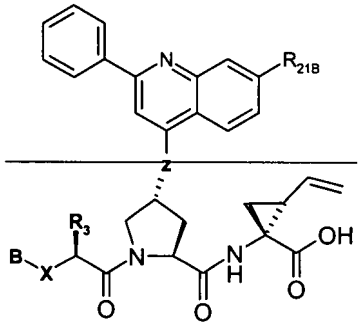
50. (twice amended) A compound according to claim 45 represented by the formula:

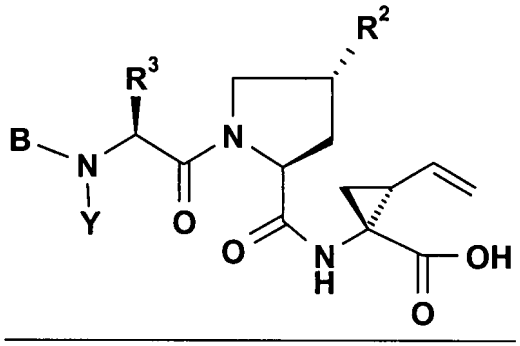


wherein **B**, **R^3**, **R^2**, **R^1** are as defined below:

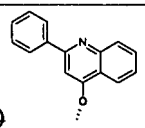
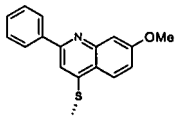
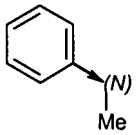
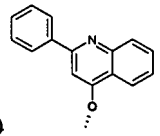
Table 2 Cpd #	B	R^3	R^2	R^1 anti to carboxy
~~and~~ 203	Boc	*t*-Bu		vinyl 1*R*, 2*R*

65. A compound according to claim 45 represented by the formula:





wherein **B-N(Y)-**, ~~X~~, ~~R_3~~ R^3, ~~z and R_{21B}~~ and R^2 are as defined below:

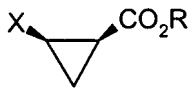
Table 10 Cpd #	B-~~X~~-N(Y)-	~~R_3~~R^3	~~Z~~R^2	~~R_{21B}~~
1001	Ph-N(Me)-	*i*-Pr		~~H;~~
1002	Boc-NH-	*t*-Bu	~~S~~ 	~~OMe;~~
and 1003		*i*-Pr		—

REMARKS

Claims 1-26, 28-80 and 84-87 are pending.

I. Restriction Requirement

Applicants maintain their traversal of the restriction between the final product compounds of Groups I-VII and the intermediate compounds of Group XI (Claims 76-79). The Examiner maintains this restriction on the basis that newly cited Ishikawa et al. (JP 05-155827) teaches the use of the same intermediate compounds as endothelin antagonists. However, the compounds disclosed in Ishikawa are cis-2-aminocyclopropane-carboxylic acid derivatives of the formula I:



in which X is an amino or protected amino group and R is a protecting group. It is clear that these compounds are entirely different and structurally distinct from the intermediates of Group XI in which the amino and carboxyl group are bonded to the same ring carbon atom. Thus, it is clear that the compounds of Group XI do not correspond to the compounds of Ishikawa. Moreover, the compounds of Ishikawa are disclosed as intermediates to prepare endothelin antagonist peptides. Thus, there is clearly no reasonable expectation that the structurally different compounds of Group XI would be useful in any synthetic preparation technique disclosed in Ishikawa, and the Examiner has not identified any disclosure in Ishikawa supporting this theory. Accordingly, the Examiner is respectfully requested to reconsider and withdraw this part of the restriction requirement.

Applicants appreciate the Examiner's indication that the process claims will be rejoined in the examination at such time when the elected compounds are found to be allowable. On page 3, the Examiner does state that "such condensation reactions are well-known in the art by applicants' own admission (Specification at page 30, line 14)." For the record, the specification mentions only that the P1, P2 and P3 groups can be linked by "well known peptide coupling techniques." Thus, these techniques may be well-known in a general sense, but this is certainly no admission concerning the patentability of the specifically claimed processes all directed to preparing a peptide analog of formula (I) according to claim 1.

II. Rejection Under 35 USC 112, Second Paragraph

At pages 4-5 of the Office Action, various claims are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite, for the following reasons:

(1) The use of the transitional word "comprising" in claim 1;

(2) The definitions for the B substituent in various claims, the Examiner suggesting that the word "derivative" be inserted into the claims at various locations for the purpose of clarity;

(3) Claim 30 refers back to itself for a definition;

(4) Claim 32 lacks antecedent basis in claim 29 for "halo";

(5) The definitions of P1 in claims 36, 37, 45 and 46, are inconsistent with claim 1;

(6) The phrase "such as" in claim 47;

(7) The identification of compounds by compound numbers in claims 49, 51, 53, 55, 57, 59, 61 and 63; and

(8) The use of the variables X and Y in claim 65 .

Applicants have amended the claims to specifically address items (1) through (6) and (8) raised by the Examiner. With respect to item (5), Applicants have added hydrogen (H) to the definition of R^1 for consistency with claim 1, this being identical to the previous language "optionally substituted with R^1."

With respect to item (7), Applicants traverse. Applicants submit that these claims do particularly point out and distinctly claim the subject matter of the invention since all the numbered compounds are specifically and clearly identified by structure in the preceding claim. Applicants are not aware of any regulation prohibiting the use of compound numbers in a claim when the compound numbers clearly identify the compound intended.

In view of the above, the Examiner is respectfully requested to reconsider and withdraw this rejection.

III. Provisos

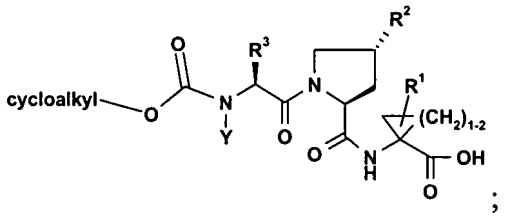
Turning to the Examiner's note with respect to the provisos, the only proviso Applicants could identify in claim 1 is in the definition of B, following the definition of R_5:
"with the proviso that when R_4 is an amide (*derivative*) or a thioamide (*derivative*), R_4 is not (ii) cycloalkoxy;".

As is apparent from the reading of this proviso, there is a typographical mistake in that R_4 cannot be an amide or a thioamide in the claim. Indeed, this proviso should read: "with the proviso that when **B** is a carboxyl derivative, an amide derivative or a

thioamide derivative, R_4 is not a cycloalkoxy.", and claim 1 has been so amended.

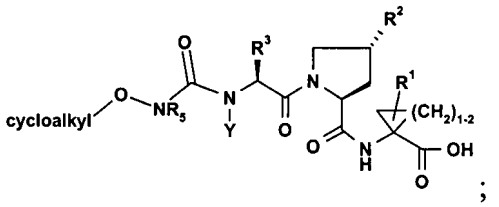
This proviso is needed to exclude compounds that are chemically unlikely or unstable. In this context, Applicants have added the carboxyl derivative to this proviso:

if **B** is a carboxyl of formula R_4-O-C(O)- and if R_4 is C_{3-7} cycloalkoxy; then the resulting structure would be:



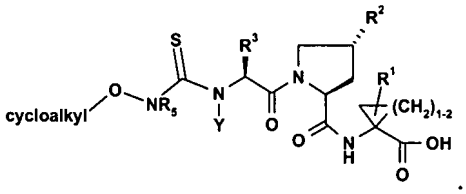
;

if **B** is an amide of formula R_4-N(R_5)-C(O)- and if R_4 is C_{3-7} cycloalkoxy; then the resulting structure would be:



;

if **B** is a thioamide of formula R_4-N(R_5)-C(S)- and if R_4 is C_{3-7} cycloalkoxy; then the resulting structure would be:



.

This proviso in claim 1 was not used up to eliminate compounds known to lack utility or

to bring the claims outside the scope of known prior art, as suggested by the Examiner but only to eliminate compounds that are likely to be chemically unstable.

IV. Claim Objections

Various claims are objected to for the following reasons:

(1) Claim 1, the definition of Het embraces heterocycles that are non-elected under the terms of the Restriction Requirement. Likewise, claims 62 and 87 contain non-elected heterocycles.

(2) Claims 15, 19 and 46 contain parentheticals for terms defined in the specification;

(3) Claim 29 has a typo and claim 50 requires the deletion of "and".

Applicants have amended the claims to specifically address items (2) and (3).

With respect to item (1), although the Examiner is correct that these other 5-membered heterocycles are not embraced by Group II of the Restriction Requirement, Applicants submit that these other related compounds are most appropriately placed within elected Group II and would not constitute an undue examination burden on the Examiner. Applicants respectfully point out that the Examiner's Restriction Requirement set forth in the Office Action of 7/26/00 does not contain any group that would cover these claimed compounds, i.e., in which R_{20} contains a pyridinyl or quinolyl group and Het is a 5-membered heterocycle other than those listed by the Examiner in Group II. Accordingly, given the structural relationship of the compounds - the same R_{20} group containing a pyridinyl or quinolyl (which R_{20} group likewise is not covered by any other Group of the restriction) and all having a 5-membered heterocycle in the

definition of Het – Applicants submit that all these related compounds should be examined together in Group II. No other Group of the Restriction Requirement contain compounds that are more closely related.

In addition, Applicant submit that it would not be an undue burden to examine all the claimed compounds given their structural relationship. As the Examiner is aware, it is the R_{20} pyridine or quinoline group that will control the classification, not the 5-membered heteroring - i.e., all the claimed compounds will be classified in Class 546 as indicated for Group II.

For the above reasons, Applicants strongly believe that all the claimed subject matter should be examined together. If the Examiner maintains this requirement, the Examiner is respectfully requested to identify which Group of the Restriction Requirement would cover the compounds that the Examiner would have Applicants cancel from the claims and provide reasons as to why these compounds to be canceled are more appropriately examined in such other Group.

Applicants submit that the claim objection at the top of page 7 of the Office Action is now moot since all the claim rejections are believed to have been overcome.

Conclusion

In view of the above amendments and remarks, Applicants respectfully submit that this application is now in condition for allowance and earnestly request such action.

If any points remain at issue which can best be resolved by way of a telephonic or personal

interview, the Examiner is kindly requested to contact the undersigned attorney at the local telephone number listed below.

Respectfully submitted,

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